DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Carol M. Moore
Vice President, Quality Assurance/Regulatory Affairs
Bayer Corporation
Biologics Product Division
800 Dwight Way
P.O. Box 1986
Berkeley, California 94701-1986

Dear Ms. Moore:

The Food and Drug Administration (FDA) conducted inspections of Bayer Corporation's (Bayer's) manufacturing facilities located in Clayton, North Carolina, between September 25 and November 17, 2000, and March 13 and March 21, 2001, and in Berkeley, California, between November 6 and December 7, 2000. During the inspections, FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and deviations from the applicable standards and requirements of Subchapter C Parts 210 and 211, and Subchapter F Parts 600-680, Title 21, Code of Federal Regulations, (21 CFR). The deviations noted on the Form FDA 483s, Inspectional Observations, issued at the conclusion of the inspections include, but are not limited to the following:

1. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192], as follows:

   a) Investigations into pyrogen failures for Prolastin Lots [ ] were limited to the [ ] operation and did not include any processes prior to the [ ]

b) Investigations into container integrity defects for finished product glassware lots [ ] were limited to Prolastin lo[ ] and failed to address other finished product lots which may have used the implicated lots of glassware.

c) Ten lots of ultrafiltered clarified tissue culture fluid (UFTCF) material that exceeded the bioburden limit of not more than [ ] were released for further processing without determining an assignable cause for the increased microbial load.

d) Investigations into microbial excursion results for the water for injection (WFI) loops in the [ ] facility buildings [ ] are incomplete in that there is no documentation of the recommendations for further investigations, corrective actions, and follow-up.

2. Failure to establish and follow written procedures for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)] in that:

a) The cleaning of the ultrafiltration/diafiltration (UF/DF) unit used in the manufacture of [ ] has not been adequately validated.

b) The UF/DF filter cartridges have no established maximum number of uses.

3. Failure to ensure that reprocessed batches of product will conform with all established standards, specifications, and characteristics [21 CFR 211.115(a)] in that there were no written procedures and validation data that support the reprocessing and reworking of Albumin for both proteinaceous material (PM) and potential glass fragments.

4. Failure to maintain and/or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to posses and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100]. For example:

a) The batch production record (BPR) [ ] entitled "Additional Precautionary Sterile Filtration for Fraction V, IGIV and Placebo Bulks," states the procedure is [ ] However, the BPR does not limit the number of filtrations. In addition, there is no data to support that the procedure was adequately validated.

b) The standard operating procedure (SOP) entitled "Error and Accident Policy for Manufacturing Locations for Bayer Biological Products," was not followed in that errors and accidents were not reported to the FDA within the established 45 day timeframe.

c) The Quality Assurance procedure entitled "The Discrepancy Event Reporting (DER) System," is inadequate in that the procedure provides no timeframes for the completion and closure of corrective actions.

d) The SOP entitled "Environmental Monitoring Sampling/Handling/Reporting," was not followed in that monthly excursion status reports have not been generated since April 4, 2000. In addition, no other procedures for tracking excursions have been implemented.

5. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR 211.160(b)] in that:

   a) There is no scientific rationale or procedure for placing the [ ] [ ] sometimes several times, in order to obtain the required pH reading.

   b) There is no assurance that the quantity of bulk and finished product samples pulled for testing are representative of the lots.

6. Failure to establish and follow written procedures applicable to the quality control unit [21 CFR 211.22(d)]. For example:

   a) There is no written procedure in place to track all batch record corrections, explanations, or required deviations from manufacturing.

   b) The SOP entitled "QA Release Department Review of Batch Production Records and Test Results," is inadequate in that it allows manufacturing supervisors to make changes to batch records without the knowledge or consultation of the manufacturing employees that were involved in the discrepancies.

We acknowledge receipt of your firm's two written responses dated January 8, 2001,with cover letters dated January 12, 2001, and the May 14, 2001, and June 8, 2001, responses which address the inspectional observations on the Form FDA 483s issued at the close of the inspections. Our comments and requests for additional information will be addressed under separate cover.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishments are in compliance with all requirements of the federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction, and/or civil money penalties.

Please notify this office in writing within 15 working days of receipt of this letter, of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions have not been completed, please state the time within which the corrections will be completed. Your reply should be sent to the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448; Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Ms. Mary A. Malarkey, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

John M. Taylor
Director
Office of Enforcement